same changes. It is submitted that no new matter has been introduced by way of these amendments. Consideration of the claims is respectfully requested in light of the following remarks.

Applicant notes with appreciation the Examiner's previous indication that claims 3, 11, 13 and 15 were objected to as being dependent on rejected base claims. Applicant would like to present the following arguments regarding the patentability of the remaining claims over the previously cited art, namely Burger ("Regiospecific Reactions with ω-carboxy-α-amino acids -- A Simple Synthesis of Aspartame", *Chemmiker Zeitlung*, 1990, 114(7-8), pp. 249-251) and Claude (U.S. Patent No. 5,510,508).

All of the arguments advanced in previous responses are incorporated by reference herein. Instead of presenting said arguments again in this paper, Applicant would like to directly address the issue at which Applicant and the Examiner have reached an impasse, namely whether the presently claimed method of synthesizing neotame is obvious in light of what is known about the synthesis of aspartame. Applicant submits that the simple answer to that query is that the presently claimed method of synthesizing neotame is not obvious. In fact, given the vast differences between neotame and aspartame (structural, physical, chemical), no assumptions can fairly be made regarding the behavior of one based on the behavior of the other. In the same way, no assumptions can fairly be made regarding the synthetic routes used to obtain these different materials. In other words, given what is known about both aspartame and neotame (and likewise the starting materials used to synthesize them), one of ordinary skill in this art would have no reasonable expectation of achieving similar results in a given application when using one of the materials based on the performance of the other of the materials in the same

application. Applicant has now prepared a §1.132 declaration of Dr. Indra Prakash, the named inventor in this case; Dr. Prakash confirms the statements made above.

Lending credence to the notion that one of ordinary skill in this art would have no reasonable expectation of achieving similar results in the synthesis of neotame, as compared to those achieved in the synthesis of aspartame, is the recent discovery of the Applicant that the present invention as originally conceived was not entirely workable. More specifically, Applicant has realized that the synthesis of neotame through an oxazolidinone derivative can be accomplished only when using ketones; the use of aldehydes simply does not work. Accordingly, Applicant has now amended the entire application to be limited to the use of ketones. Dr. Prakash details this recent discovery, as well as opines upon its significance, in his §1.132 declaration.

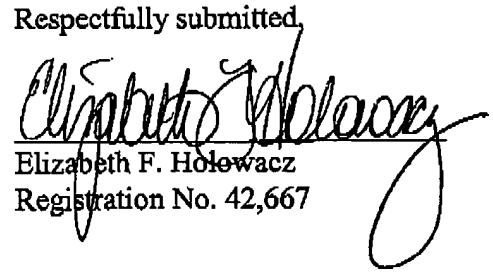
Aspartame can be synthesized via oxazolidinones using both ketones and aldehydes. According to the Examiner's line of reasoning, neotame, since it is an "analog" of aspartame, should be capable of being synthesized in the same manners. But, as noted above, the same syntheses are not possible. The differences that exist between neotame and aspartame and, indeed, between their respective starting materials, i.e., N-(3,3-dimethylbutyl)-L-aspartic acid and L-aspartic acid, are significant enough to result in the failure of a given synthetic route to be applied to both neotame and aspartame. That is, contrary to the Examiner's characterization of the substitution of N-(3,3-dimethylbutyl)-L-aspartic acid for L-aspartic acid as a "trivial" modification, such a substitution has profound effects. The former material cannot be paired with an aldehyde to form an oxazolidinone in the ultimate synthesis of neotame, while the latter can be so paired to form aspartame. Clearly, this difference evidences the lack of reasonable expectation of

success that one of ordinary skill in this art would have when working with neotame as opposed to aspartame or when synthesizing neotame as opposed to aspartame. In sum, Applicant again earnestly submits that the present invention is not obvious in light of the cited art.

In view of the foregoing amendments and remarks, favorable consideration and passage to issue of the present case is respectfully requested. Should the Examiner believe that issues remain outstanding, the Examiner is respectfully requested to contact Applicant's undersigned attorney in an effort to resolve such issues and advance the case to issue.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



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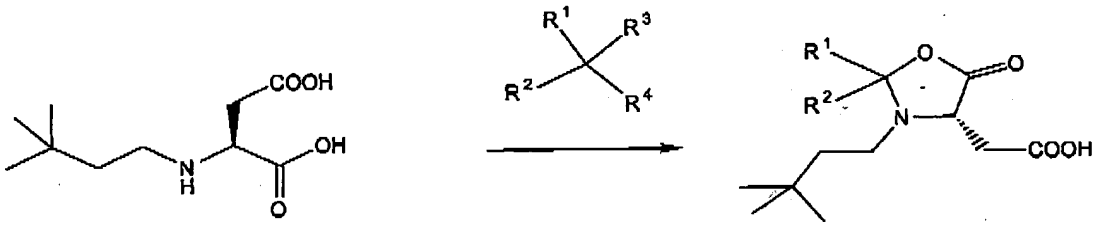
VERSION SHOWING CHANGES MADE TO SPECIFICATION

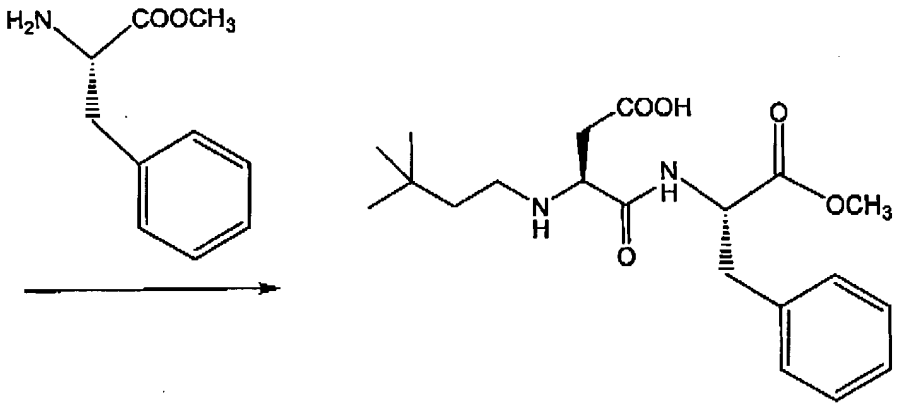
The paragraphs starting at page 5, line 1, and ending at page 7, line 16, have been amended as follows:

According to the present inventive method, neotame is synthesized by reacting N-(3,3-dimethylbutyl)-L-aspartic acid and a [carbonyl or activated carbonyl compound] ketone in a solvent for a time and at a temperature sufficient to produce an oxazolidinone derivative and by reacting the oxazolidinone derivative and phenylalanine or phenylalanine methyl ester in the solvent for a time and at a temperature sufficient to produce N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

The present invention relates to the regioselective formation of N-alkylated α-aspartyl amides via the use of [carbonyl compounds] ketones, and particularly to the use of such regioselective processing to obtain oxazolidinone derivatives which can react with L-phenylalanine methyl ester in a solvent with or without acid and/or a catalyst to yield N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester (neotame) with the usual work-up. The present synthetic method is represented by the following reaction scheme:



wherein R^1 is [H or] R^2, R^2 is [H or] Ph or CX_3, X is H, Cl, Br or F, R^3 and R^4 taken together is =O, or R^3 and R^4 are the same and are OCH_3 or OC_2H_5



According to the present invention, neotame is synthesized by reacting N-(3,3-dimethylbutyl)-L-aspartic acid and a [carbonyl or activated carbonyl compound] ketone in a first solvent for a time and at a temperature sufficient to produce an oxazolidinone derivative and by reacting the oxazolidinone derivative and phenylalanine or phenylalanine methyl ester in a second solvent for a time and at a temperature sufficient to produce N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

According to the first step of the present inventive method, an admixture of N-(3,3-dimethylbutyl)-L-aspartic acid and a [carbonyl or activated carbonyl compound] ketone are reacted in a first solvent for a time and at a temperature sufficient to produce an oxazolidinone derivative.

[Carbonyl compounds (aldehydes and ketones)] Ketones of the formula $R^1R^2C=O$ or [activated carbonyl compounds (acetals of aldehydes and ketones)] acetals of ketones of the formula $CR^1R^2R^3R^4$, wherein R^1 is [H or] R^2, R^2 is [H or] Ph or CX_3, X is H, Cl, Br or F, R^3 and R^4 taken together is =O, or R^3 and R^4 are the same and are OCH_3 or OC_2H_5 are suitable for use in the present invention. Ph is phenyl or substituted phenyl. Suitable [carbonyl compounds] ketones include, without limitation, hexafluoroacetone, 1,1,1-trifluoroacetone, [trichloroacetaldehyde, tribromoacetaldehyde,] hexachloroacetone, [formaldehyde, paraformaldehyde, benzaldehyde, substituted benzaldehydes] and combinations thereof.

N-(3,3-dimethylbutyl)-L-aspartic acid is prepared as described in U.S. Patent No. 6,077,962, the disclosure of which is incorporated by reference herein. The [carbonyl compounds] ketones are readily available starting materials. The N-(3,3-dimethylbutyl)-L-aspartic acid and the [carbonyl or activated carbonyl compound] ketone are typically combined in a molar ratio ranging from about 1:1 to about 1:4.

The paragraph at page 8, lines 1-11, has been amended as follows:

In certain embodiments of the present invention, a catalyst may be present during the reaction of N-(3,3-dimethylbutyl)-L-aspartic acid and the [carbonyl compound] ketone. Suitable catalysts include, without limitation, p-toluenesulfonic acid. In certain embodiments of the present invention, an acid may be present during the reaction of N-(3,3-dimethylbutyl)-L-aspartic acid and the [carbonyl compound] ketone. Suitable acids include, without limitation, formic acid, acetic acid, p-toluenesulfonic acid, methane sulfonic acid, 10-camphorsulfonic acid and combinations thereof.

The paragraphs starting at page 13, line 14, and ending at page 14, line 22, have been deleted.

The paragraphs starting at page 14, line 24, and ending at page 16, line 3, have been amended as follows:

EXAMPLE [6] 3

2-[(4S)-3-(3,3-dimethylbutyl)-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolan-4-yl]acetic acid

A gas flow of hexafluoroacetone is blown at a moderate rate at room temperature onto an intensely stirred suspension of 10 mmol of N-(3,3-dimethylbutyl)-L-aspartic acid in 20 ml 1,4-dioxane. A clear solution is formed overnight. The solvent was removed in vacuo, and the oily residue was confirmed to be an almost quantitative amount of 2-[(4S)-3-(3,3-dimethylbutyl)-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolan-4-yl]acetic acid by NMR.

EXAMPLE [7] 4

N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester

2-[(4S)-3-(3,3-dimethylbutyl)-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolan-4-yl]acetic acid (2 mmol) and L-phenylalanine 1-methyl ester (2 mmol) were dissolved in tetrahydrofuran (15 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo to yield an oil. A white solid, confirmed to be neotame by NMR, was obtained after stirring the oil in water overnight. Neotame was obtained in 90% yield.

EXAMPLE [8] 5

N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester

L-phenylalanine 1-methyl ester hydrochloride (10 mmol), tetrahydrofuran (15 ml) and sodium acetate (NaOAc, 10 mmol) were loaded into a 50 ml flask. The mixture was stirred at room temperature for 15 minutes. A solution of 2-[(4S)-3-(3,3-dimethylbutyl)-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolan-4-yl]acetic acid (10 mmol) in tetrahydrofuran (10 ml) was added to the mixture. The mixture was then stirred at room temperature for 24 hours. The solvent was removed in vacuo to yield a residue. The residue was stirred in water overnight at room temperature. The precipitated solid was filtered, washed with water and dried to yield neotame in 90% yield.

EXAMPLE [9] 6

2-[(4S)-3-(3,3-dimethylbutyl)-2,2-dimethyl-5-oxo-1,3-oxazolan-4-yl]acetic acid

VERSION SHOWING CHANGES MADE TO CLAIMS

1. (Amended) A process of synthesizing N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester comprising the steps of:

(a) reacting an admixture of N-(3,3-dimethylbutyl)-L-aspartic acid and a [carbonyl compound or an activated carbonyl compound] ketone in a first solvent for a time and at a temperature sufficient to produce an oxazolidinone derivative; and

(b) reacting an admixture of the oxazolidinone derivative and L-phenylalanine or L-phenylalanine methyl ester in a second solvent for a time and at a temperature sufficient to produce N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

2. (Amended) The process according to claim 1, wherein the [carbonyl compound] ketone is selected from the group consisting of hexafluoroacetone, [trichloroacetaldehyde, tribromoacetaldehyde,] hexachloroacetone, [formaldehyde, paraformaldehyde, benzaldehyde, substituted benzaldehydes] and combinations thereof.

3. (Twice Amended) The process according to claim 1, wherein the [carbonyl compound] ketone is selected from the group consisting of dimethyl or diethyl acetals of hexafluoroacetone, [trichloroacetaldehyde, tribromoacetaldehyde,] hexachloroacetone, [formaldehyde, benzaldehyde, substituted benzaldehydes] and combinations thereof.

5. (Amended) The process according to claim 1, wherein the ratio of N-(3,3-dimethylbutyl)-L-aspartic acid to the [carbonyl compound] ketone is from about 1:1 to about 1:4.

10. (Amended) The process according to claim 1, wherein the admixture of N-(3,3-dimethylbutyl)-L-aspartic acid and a [carbonyl compound or an activated carbonyl compound] ketone further comprises a catalyst.

12. (Amended) The process according to claim 1, wherein the admixture of N-(3,3-dimethylbutyl)-L-aspartic acid and a [carbonyl compound or an activated carbonyl] ketone further comprises an acid.